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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/753,169	01/02/2001	Cy A. Stein	55669-A-PCT-US/JPW/GJC	9695

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EXAMINER
EPPS FORD, JANET L

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/19/2004

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/753,169	STEIN ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,9 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,9 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 5, 9, and 43 are currently pending in the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claim Rejections - 35 USC § 112

3. Claim 43 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the pharmaceutical compositions of the instant invention in an *in vitro* method, does not reasonably provide enablement for using the claimed pharmaceutical compositions *in vivo* for therapeutic purposes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim, for the reasons of record set forth in the Office Action mailed 6-18-03.

Applicant's arguments filed 3-8-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that working examples are provided in the specification, and that the claim language distinguishes over oligonucleotides of unknown length that do not inhibit translation of bcl-xL encoding mRNA. Contrary to Applicant's assertions the claims do not recite any particular length of oligonucleotide. Applicants argue tat both the Branch does not teach that an antisense active in vitro has not activity in vivo, merely that it may be a different activity. However, contrary to Applicant's conclusion about Branch, Applicant's own conclusion states a level of unpredictability regarding the behavior of antisense oligonucleotides in vivo in comparison to their behavior in vitro.

Applicants refer to Crooke, and state that the disclosure of Crooke shows numerous examples of antisense with in vivo activity, and discusses antisense in vitro that have been successful in vivo. However, Applicants are reminded that Crooke also stated that extrapolations from in vitro uptake studies to predictions about in vivo pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all in vitro uptake data, one cannot predict in vivo pharmacokinetics of the compounds based on in vitro studies."

Applicants further state that dosage determination is a standard clinical skill in the art, and although possibly requiring some experimentation, does not require undue experimentation. Moreover, Applicants argue that only a "reasonable correlation between the disclosed in vitro utility and in vivo activity is required for enablement," which they have shown, and the known role of bcl-xL in intimal lesion formation. However, the known role for bcl-xL inhibition for reducing intimal lesion formation by antisense has been demonstrated using the oligonucleotide set forth in Gibbons et al. and Pollman et al. (cited in a previous Office Action) which comprise SEQ ID NO: 2 according to the present invention. There is no correlative evidence that would indicate that the behavior of an antisense oligonucleotide comprising SEQ ID NO: 2 would be able to predict the behavior of all oligonucleotides encompassed by the instant claims.

As stated in the prior Office Action, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the delivery of antisense *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The deficiencies in

the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

4. Claim 43 remain rejected, and claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the Official Action mailed 1-05-04.

5. Applicant's arguments filed 3-08-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that by amending claim 5 to recite "consisting essentially" instead of comprising, and to recite a functional characteristic of the claimed oligonucleotide, the claims are now more clearly defined, and the rejection should be withdrawn. First, it is noted that the transitional phrase "consisting essentially of" limits the scope of the claims to the specified matter, and those that do not materially affect the basic and novel characteristics of the claimed invention, see MPEP § 2111.03. However, the specification as filed do not define what factors or structural features that may be added to the claimed oligonucleotides, wherein such additions do not materially affect the basic and novel characteristics of the claimed invention. Without defining what other features may be added to the claimed oligonucleotides, such that the novel or basic characteristics are maintained, the ordinary skilled artisan would have to perform more experimentation in order to identify what features or structural modifications are encompassed by the instant claims, wherein these features do not materially affect the basic and novel characteristics of the claimed invention.

Since, it is clear that further experimentation is required to identify what factors or modifications are encompassed by the instant invention, such that the claimed invention "consist essentially" of the claimed oligonucleotides, and said factors or modifications, Applicants were not in possession of the full scope of compounds and compositions encompassed by the instant invention.

Double Patenting

6. Claims 5, 9 and 43 remain provisionally rejected under the judicially created doctrine of double patenting over claims 9, 36-50, 53-54, 58, and 61-62 of copending Application No. 09/832,648 in view of Manoharan et al. Sanghvi et al., Matteucci et al. and Arnold et al. for the reasons of record set forth in the prior Office Action mailed 6-18-03. Applicant's arguments filed 3-08-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the claims of copending application 09/832,648 recite elements, namely 2'-Ome modifications, that are unobvious over the claims as herein amended. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection. Contrary to Applicant's assertions, the claims of the instant application and those of the copending application, are all directed to antisense oligonucleotides targeting bcl-xL encoding mRNA comprising modifications which enhance the biological properties of the oligonucleotide. As stated in the prior Office Action, the specification as filed describe analogs of the antisense oligonucleotides of the present invention which encompass 2'-OMe modified oligonucleotides, see page 10, lines 3-8, specifically 2'-O-alkyl, which has been shown in many instances to increase the resistance of an oligonucleotide to degradation. Therefore, the claims of

the copending application represent an obvious preferred alternative embodiment of the currently claimed invention in the instant application.

7. Claims 5, 9, and 43 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37-43, 51-53, 58, and 61-62 of copending Application No. 10/160,344. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and those of the copending application are both drawn to antisense oligonucleotide compounds or compositions comprising the nucleotide sequence of SEQ ID NOs: 1, and 3-13, and compositions thereof. The subject matter of the claims of the instant application and that of the claims of the copending application differ to the extent that the claims of the instant application are drawn to antisense oligonucleotides conjugated to a peptide, and those of the is co-extensive in scope, except in certain cases the claims of the instant application recite antisense compounds, and compositions thereof, drawn to specific nucleotide sequences such as the nucleotide sequence according to sequence G of Figure 1 (i.e. SEQ ID NO: 7), or sequences C, D, E, F, G, I, and M of Figure 1 (or SEQ ID NO: 3-7, 9 and 19, however the claims of the co-pending application recite SEQ ID NO: 1-13. The claims of the instant application represent an obvious variation of the invention recited in the claims of the co-pending application since it is clear that the claimed oligonucleotides that inhibit bcl-xL encoding mRNA sequence and are conjugated to a peptide are obvious preferred alternative embodiments of the claimed invention, see pages 14-15 of the instant application and that also of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE